

<110> SZKUDLINSI, Mariusz W.
WIENTRAUB, Bruce D.

<120> Follicle Stimulating Hormone Superagonists

<130> 056815-5001-WO

<150> US 60/554,419

<151> 2004-03-19

<160> 24

<170> PatentIn version 3.3

<210> 1

<211> 92

<212> PRT

<213> Homo sapiens

<400> 1

Ala Pro Asp Val Gln Asp Cys Pro Glu Cys Thr Leu Gln Glu Asn Pro
1 5 10 15

Phe Phe Ser Gln Pro Gly Ala Pro Ile Leu Gln Cys Met Gly Cys Cys
20 25 30

Phe Ser Arg Ala Tyr Pro Thr Pro Leu Arg Ser Lys Lys Thr Met Leu
35 40 45

Val Gln Lys Asn Val Thr Ser Glu Ser Thr Cys Cys Val Ala Lys Ser
50 55 60

Tyr Asn Arg Val Thr Val Met Gly Gly Phe Lys Val Glu Asn His Thr
65 70 75 80

Ala Cys His Cys Ser Thr Cys Tyr Tyr His Lys Ser
85 90

<210> 2

<211> 111

<212> PRT

<213> Homo sapiens

<400> 2

Asn Ser Cys Glu Leu Thr Asn Ile Thr Ile Ala Ile Glu Lys Glu Glu
1 5 10 15

Cys Arg Phe Cys Ile Ser Ile Asn Thr Thr Trp Cys Ala Gly Tyr Cys
20 25 30

Tyr Thr Arg Asp Leu Val Tyr Lys Asp Pro Ala Arg Pro Lys Ile Gln
35 40 45

Lys Thr Cys Thr Phe Lys Glu Leu Val Tyr Glu Thr Val Arg Val Pro
50 55 60

Gly Cys Ala His His Ala Asp Ser Leu Tyr Thr Tyr Pro Val Ala Thr
65 70 75 80

Gln Cys His Cys Gly Lys Cys Asp Ser Asp Ser Thr Asp Cys Thr Val
85 90 95

Arg Gly Leu Gly Pro Ser Tyr Cys Ser Phe Gly Glu Met Lys Glu
100 105 110

<210> 3
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino terminal extension; potential glycosylation recognition
site

<400> 3

Ala Asn Ile Thr Val
1 5

<210> 4
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino terminal extension; potential glycosylation recognition
site

<400> 4

Ala Asn Ile Thr Val Asn Ile Thr Val
1 5

<210> 5
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> Negatively charged amino acid insert to modify protein half-life

<400> 5

Gly Glu Phe Thr
1

<210> 6
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Negatively charged amino acid insert to modify protein half-life
<400> 6

Gly Glu Phe Thr Thr
1 5

<210> 7
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> FSH segment with negatively charged amino acid insert to modify protein half-life
<400> 7

Ala Asp Pro Gly Glu Phe Thr Val Gln Asp Cys
1 5 10

<210> 8
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> FSH segment with negatively charged amino acid insert to modify protein half-life
<400> 8

Ala Asp Pro Gly Glu Phe Thr Thr Gln Asp Cys
1 5 10

<210> 9
<211> 97
<212> PRT
<213> Artificial Sequence

<220>
<223> Mutated FSH alpha mature peptide sequence with N-terminal extension
<400> 9

Ala Asn Ile Thr Val Ala Pro Asp Val Gln Asp Cys Pro Glu Cys Thr
1 5 10 15

4/22

Leu Gln Glu Asn Pro Phe Phe Ser Gln Pro Gly Ala Pro Ile Leu Gln
20 25 30

Cys Met Gly Cys Cys Phe Ser Arg Ala Tyr Pro Thr Pro Leu Arg Ser
35 40 45

Lys Lys Thr Met Leu Val Gln Lys Asn Val Thr Ser Glu Ser Thr Cys
50 55 60

Cys Val Ala Lys Ser Tyr Asn Arg Val Thr Val Met Gly Gly Phe Lys
65 70 75 80

Val Glu Asn His Thr Ala Cys His Cys Ser Thr Cys Tyr Tyr His Lys
85 90 95

Ser

<210> 10

<211> 97

<212> PRT

<213> Artificial Sequence

 $\langle 220 \rangle$

<223> Mutated FSH alpha mature peptide sequence with N-terminal extension

<400> 10

Ala Asn Ile Thr Val Ala Pro Asp Val Gln Asp Cys Pro Glu Cys Thr
1 5 10 15

Leu Gln Arg Asn Pro Phe Phe Ser Arg Pro Gly Ala Pro Ile Leu Gln
20 25 30

Cys Met Gly Cys Cys Phe Ser Arg Ala Tyr Pro Thr Pro Leu Arg Ser
35 40 45

Lys Lys Thr Met Leu Val Gln Lys Asn Val Thr Ser Glu Ser Thr Cys
50 55 60

Cys Val Ala Lys Ser Tyr Asn Arg Val Thr Val Met Gly Arg Phe Lys
65 70 75 80

Val Glu Asn His Thr Ala Cys His Cys Ser Thr Cys Tyr Tyr His Lys
85 90 95

Ser

<210> 11
 <211> 101
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Mutated FSH alpha mature peptide sequence with N-terminal extension

<400> 11

Ala Asn Ile Thr Val Asn Ile Thr Val Ala Pro Asp Val Gln Asp Cys
 1 5 10 15

Pro Glu Cys Thr Leu Gln Glu Asn Pro Phe Phe Ser Gln Pro Gly Ala
 20 25 30

Pro Ile Leu Gln Cys Met Gly Cys Cys Phe Ser Arg Ala Tyr Pro Thr
 35 40 45

Pro Leu Arg Ser Lys Lys Thr Met Leu Val Gln Lys Asn Val Thr Ser
 50 55 60

Glu Ser Thr Cys Cys Val Ala Lys Ser Tyr Asn Arg Val Thr Val Met
 65 70 75 80

Gly Gly Phe Lys Val Glu Asn His Thr Ala Cys His Cys Ser Thr Cys
 85 90 95

Tyr Tyr His Lys Ser
 100

<210> 12
 <211> 101
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Mutated FSH alpha mature peptide sequence with N-terminal extension

<400> 12

Ala Asn Ile Thr Val Asn Ile Thr Val Ala Pro Asp Val Gln Asp Cys
 1 5 10 15

Pro Glu Cys Thr Leu Gln Arg Asn Pro Phe Phe Ser Arg Pro Gly Ala
 20 25 30

6/22

Pro Ile Leu Gln Cys Met Gly Cys Cys Phe Ser Arg Ala Tyr Pro Thr
 35 40 45

Pro Leu Arg Ser Lys Lys Thr Met Leu Val Gln Lys Asn Val Thr Ser
 50 55 60

Glu Ser Thr Cys Cys Val Ala Lys Ser Tyr Asn Arg Val Thr Val Met
 65 70 75 80

Gly Arg Phe Lys Val Glu Asn His Thr Ala Cys His Cys Ser Thr Cys
 85 90 95

Tyr Tyr His Lys Ser
 100

<210> 13
 <211> 111
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Mutated FSH beta mature peptide sequence

<400> 13

Asn Ser Cys Glu Leu Thr Asn Ile Thr Ile Ala Ile Glu Lys Glu Glu
 1 5 10 15

Cys Arg Phe Cys Ile Ser Ile Asn Thr Thr Trp Cys Ala Gly Tyr Cys
 20 25 30

Tyr Thr Arg Asp Leu Val Tyr Lys Asp Pro Ala Arg Pro Lys Ile Gln
 35 40 45

Lys Thr Cys Thr Phe Lys Glu Leu Val Tyr Glu Thr Val Arg Val Pro
 50 55 60

Gly Cys Ala His His Ala Asp Ser Leu Tyr Thr Tyr Pro Asn Ala Thr
 65 70 75 80

Gln Cys His Cys Gly Lys Cys Asp Ser Asp Ser Thr Asp Cys Thr Val
 85 90 95

Arg Gly Leu Gly Pro Ser Tyr Cys Ser Phe Gly Glu Met Lys Glu
 100 105 110

<210> 14
 <211> 111

7/22

<212> PRT

<213> Artificial Sequence

<220>

<223> Mutated FSH beta mature peptide sequence

<400> 14

Asn Ser Cys Arg Leu Thr Asn Ile Thr Ile Ala Ile Glu Lys Glu Glu
 1 5 10 15

Cys Arg Phe Cys Ile Ser Ile Asn Thr Thr Trp Cys Ala Gly Tyr Cys
 20 25 30

Tyr Thr Arg Asp Leu Val Tyr Lys Asp Pro Ala Arg Pro Lys Ile Gln
 35 40 45

Lys Thr Cys Thr Phe Lys Glu Leu Val Tyr Glu Thr Val Arg Val Pro
 50 55 60

Gly Cys Ala His His Ala Asp Ser Leu Tyr Thr Tyr Pro Asn Ala Thr
 65 70 75 80

Gln Cys His Cys Gly Lys Cys Asp Ser Asp Ser Thr Asp Cys Thr Val
 85 90 95

Arg Gly Leu Gly Pro Ser Tyr Cys Ser Phe Gly Glu Met Lys Glu
 100 105 110

<210> 15

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> Mutated FSH beta mature peptide sequence

<400> 15

Asn Ser Cys Glu Leu Thr Asn Ile Thr Ile Ala Ile Glu Lys Glu Glu
 1 5 10 15

Cys Arg Phe Cys Ile Ser Ile Asn Thr Thr Trp Cys Ala Gly Tyr Cys
 20 25 30

Tyr Thr Arg Asp Leu Val Tyr Lys Asp Pro Ala Arg Pro Lys Ile Gln
 35 40 45

Lys Thr Cys Thr Phe Lys Glu Leu Val Asn Glu Thr Val Arg Val Pro
 50 55 60

Gly Cys Ala His His Ala Asp Ser Leu Tyr Thr Tyr Pro Val Ala Thr
 65 70 75 80

Gln Cys His Cys Gly Lys Cys Asp Ser Asp Ser Thr Asp Cys Thr Val
 85 90 95

Arg Gly Leu Gly Pro Ser Tyr Cys Ser Phe Gly Glu Met Lys Glu
 100 105 110

<210> 16
 <211> 111
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Mutated FSH beta mature peptide sequence

<400> 16

Asn Ser Cys Arg Leu Thr Asn Ile Thr Ile Ala Ile Glu Lys Glu Glu
 1 5 10 15

Cys Arg Phe Cys Ile Ser Ile Asn Thr Thr Trp Cys Ala Gly Tyr Cys
 20 25 30

Tyr Thr Arg Asp Leu Val Tyr Lys Asp Pro Ala Arg Pro Lys Ile Gln
 35 40 45

Lys Thr Cys Thr Phe Lys Glu Leu Val Asn Glu Thr Val Arg Val Pro
 50 55 60

Gly Cys Ala His His Ala Asp Ser Leu Tyr Thr Tyr Pro Val Ala Thr
 65 70 75 80

Gln Cys His Cys Gly Lys Cys Asp Ser Asp Ser Thr Asp Cys Thr Val
 85 90 95

Arg Gly Leu Gly Pro Ser Tyr Cys Ser Phe Gly Glu Met Lys Glu
 100 105 110

<210> 17
 <211> 121
 <212> PRT
 <213> Homo sapiens

<400> 17

Ser Arg Glu Pro Leu Arg Pro Trp Cys His Pro Ile Asn Ala Ile Leu
 1 5 10 15

9/22

Ala Val Glu Lys Glu Gly Cys Pro Val Cys Ile Thr Val Asn Thr Thr
 20 25 30

Ile Cys Ala Gly Tyr Cys Pro Thr Met Met Arg Val Leu Gln Ala Val
 35 40 45

Leu Pro Pro Leu Pro Gln Val Val Cys Thr Tyr Arg Asp Val Arg Phe
 50 55 60

Glu Ser Ile Arg Leu Pro Gly Cys Pro Arg Gly Val Asp Pro Val Val
 65 70 75 80

Ser Phe Pro Val Ala Leu Ser Cys Arg Cys Gly Pro Cys Arg Arg Ser
 85 90 95

Thr Ser Asp Cys Gly Gly Pro Lys Asp His Pro Leu Thr Cys Asp His
 100 105 110

Pro Gln Leu Ser Gly Leu Leu Phe Leu
 115 120

<210> 18
 <211> 24
 <212> PRT
 <213> Homo sapiens

<400> 18

Met Asp Tyr Tyr Arg Lys Tyr Ala Ala Ile Phe Leu Val Thr Leu Ser
 1 5 10 15

Val Phe Leu His Val Leu His Ser
 20

<210> 19
 <211> 18
 <212> PRT
 <213> Homo sapiens

<400> 19

Met Lys Thr Leu Gln Phe Phe Phe Leu Phe Cys Cys Trp Lys Ala Ile
 1 5 10 15

Cys Cys

<210> 20
 <211> 20

10/22

<212> PRT
 <213> Homo sapiens

<400> 20

Met Glu Met Leu Gln Gly Leu Leu Leu Leu Leu Leu Ser Met Gly
 1 5 10 15

Gly Ala Trp Ala
 20

<210> 21
 <211> 692
 <212> PRT
 <213> Rattus norvegicus

<400> 21

Met Ala Leu Leu Leu Val Ser Leu Leu Ala Phe Leu Gly Thr Gly Ser
 1 5 10 15

Gly Cys His His Trp Leu Cys His Cys Ser Asn Arg Val Phe Leu Cys
 20 25 30

Gln Asp Ser Lys Val Thr Glu Ile Pro Thr Asp Leu Pro Arg Asn Ala
 35 40 45

Ile Glu Leu Arg Phe Val Leu Thr Lys Leu Arg Val Ile Pro Lys Gly
 50 55 60

Ser Phe Ala Gly Phe Gly Asp Leu Glu Lys Ile Glu Ile Ser Gln Asn
 65 70 75 80

Asp Val Leu Glu Val Ile Glu Ala Asp Val Phe Ser Asn Leu Pro Lys
 85 90 95

Leu His Glu Ile Arg Ile Glu Lys Ala Asn Asn Leu Leu Tyr Ile Asn
 100 105 110

Pro Glu Ala Phe Gln Asn Leu Pro Ser Leu Arg Tyr Leu Leu Ile Ser
 115 120 125

Asn Thr Gly Ile Lys His Leu Pro Ala Val His Lys Ile Gln Ser Leu
 130 135 140

Gln Lys Val Leu Leu Asp Ile Gln Asp Asn Ile Asn Ile His Ile Val
 145 150 155 160

Ala Arg Asn Ser Phe Met Gly Leu Ser Phe Glu Ser Val Ile Leu Trp

11/22

				165						170					175	
Leu	Ser	Lys	Asn	Gly	Ile	Glu	Glu	Ile	His	Asn	Cys	Ala	Phe	Asn	Gly	.
			180					185					190			
Thr	Gln	Leu	Asp	Glu	Leu	Asn	Leu	Ser	Asp	Asn	Asn	Asn	Leu	Glu	Glu	
		195					200					205				
Leu	Pro	Asn	Asp	Val	Phe	Gln	Gly	Ala	Ser	Gly	Pro	Val	Ile	Leu	Asp	.
	210					215					220					
Ile	Ser	Arg	Thr	Lys	Val	His	Ser	Leu	Pro	Asn	His	Gly	Leu	Glu	Asn	
225					230					235					240	
Leu	Lys	Lys	Leu	Arg	Ala	Arg	Ser	Thr	Tyr	Arg	Leu	Lys	Lys	Leu	Pro	
				245					250					255		
Asn	Leu	Asp	Lys	Phe	Val	Thr	Leu	Met	Glu	Ala	Ser	Leu	Thr	Tyr	Pro	
			260					265					270			
Ser	His	Cys	Cys	Ala	Phe	Ala	Asn	Leu	Lys	Arg	Gln	Ile	Ser	Glu	Leu	
		275					280					285				
His	Pro	Ile	Cys	Asn	Lys	Ser	Ile	Leu	Arg	Gln	Asp	Ile	Asp	Asp	Met	
	290					295					300					
Thr	Gln	Ile	Gly	Asp	Gln	Arg	Val	Ser	Leu	Ile	Asp	Asp	Glu	Pro	Ser	
305					310					315					320	
Tyr	Gly	Lys	Gly	Ser	Asp	Met	Met	Tyr	Asn	Glu	Phe	Asp	Tyr	Asp	Leu	
				325					330					335		
Cys	Asn	Glu	Val	Val	Asp	Val	Thr	Cys	Ser	Pro	Lys	Pro	Asp	Ala	Phe	
			340					345					350			
Asn	Pro	Cys	Glu	Asp	Ile	Met	Gly	Tyr	Asn	Ile	Leu	Arg	Val	Leu	Ile	
		355					360					365				
Trp	Phe	Ile	Ser	Ile	Leu	Ala	Ile	Thr	Gly	Asn	Thr	Thr	Val	Leu	Val	
	370					375					380					
Val	Leu	Thr	Thr	Ser	Gln	Tyr	Lys	Leu	Thr	Val	Pro	Arg	Phe	Leu	Met	
385					390					395					400	
Cys	Asn	Leu	Ala	Phe	Ala	Asp	Leu	Cys	Ile	Gly	Ile	Tyr	Leu	Leu	Leu	
			405						410					415		

12/22

Ile Ala Ser Val Asp Ile His Thr Lys Ser Gln Tyr His Asn Tyr Ala
 420 425 430

Ile Asp Trp Gln Thr Gly Ala Gly Cys Asp Ala Ala Gly Phe Phe Thr
 435 440 445

Val Phe Ala Ser Glu Leu Ser Val Tyr Thr Leu Thr Ala Ile Thr Leu
 450 455 460

Glu Arg Trp His Thr Ile Thr His Ala Met Gln Leu Glu Cys Lys Val
 465 470 475 480

Gln Leu Arg His Ala Ala Ser Val Met Val Leu Gly Trp Thr Phe Ala
 485 490 495

Phe Ala Ala Ala Leu Phe Pro Ile Phe Gly Ile Ser Ser Tyr Met Lys
 500 505 510

Val Ser Ile Cys Leu Pro Met Asp Ile Asp Ser Pro Leu Ser Gln Leu
 515 520 525

Tyr Val Met Ala Leu Leu Val Leu Asn Val Leu Ala Phe Val Val Ile
 530 535 540

Cys Gly Cys Tyr Thr His Ile Tyr Leu Thr Val Arg Asn Pro Thr Ile
 545 550 555 560

Val Ser Ser Ser Ser Asp Thr Lys Ile Ala Lys Arg Met Ala Thr Leu
 565 570 575

Ile Phe Thr Asp Phe Leu Cys Met Ala Pro Ile Ser Phe Phe Ala Ile
 580 585 590

Ser Ala Ser Leu Lys Val Pro Leu Ile Thr Val Ser Lys Ala Lys Ile
 595 600 605

Leu Leu Val Leu Phe Tyr Pro Ile Asn Ser Cys Ala Asn Pro Phe Leu
 610 615 620

Tyr Ala Ile Phe Thr Lys Asn Phe Arg Arg Asp Phe Phe Ile Leu Leu
 625 630 635 640

Ser Lys Phe Gly Cys Tyr Glu Met Gln Ala Gln Ile Tyr Arg Thr Glu
 645 650 655

Thr Ser Ser Ala Thr His Asn Phe His Ala Arg Lys Ser His Cys Ser
660 665 670

Ser Ala Pro Arg Val Thr Asn Ser Tyr Val Leu Val Pro Leu Asn His
675 680 685

Ser Ser Gln Asn
690

<210> 22
<211> 695
<212> PRT
<213> Homo sapiens

<400> 22

Met Ala Leu Leu Leu Val Ser Leu Leu Ala Phe Leu Ser Leu Gly Ser
1 5 10 15

Gly Cys His His Arg Ile Cys His Cys Ser Asn Arg Val Phe Leu Cys
20 25 30

Gln Glu Ser Lys Val Thr Glu Ile Pro Ser Asp Leu Pro Arg Asn Ala
35 40 45

Ile Glu Leu Arg Phe Val Leu Thr Lys Leu Arg Val Ile Gln Lys Gly
50 55 60

Ala Phe Ser Gly Phe Gly Asp Leu Glu Lys Ile Glu Ile Ser Gln Asn
65 70 75 80

Asp Val Leu Glu Val Ile Glu Ala Asp Val Phe Ser Asn Leu Pro Lys
85 90 95

Leu His Glu Ile Arg Ile Glu Lys Ala Asn Asn Leu Leu Tyr Ile Thr
100 105 110

Pro Glu Ala Phe Gln Asn Leu Pro Asn Leu Gln Tyr Leu Leu Ile Ser
115 120 125

Asn Thr Gly Ile Lys His Leu Pro Asp Val His Lys Ile His Ser Leu
130 135 140

Gln Lys Val Leu Leu Asp Ile Gln Asp Asn Ile Asn Ile His Thr Ile
145 150 155 160

Glu Arg Asn Ser Phe Val Gly Leu Ser Phe Glu Ser Val Ile Leu Trp

165										170					175				
Leu	Asn	Lys	Asn	Gly	Ile	Gln	Glu	Ile	His	Asn	Cys	Ala	Phe	Asn	Gly				
			180					185					190						
Thr	Gln	Leu	Asp	Ala	Val	Asn	Leu	Ser	Asp	Asn	Asn	Asn	Leu	Glu	Glu				
		195					200					205							
Leu	Pro	Asn	Asp	Val	Phe	His	Gly	Ala	Ser	Gly	Pro	Val	Ile	Leu	Asp				
	210					215					220								
Ile	Ser	Arg	Thr	Arg	Ile	His	Ser	Leu	Pro	Ser	Tyr	Gly	Leu	Glu	Asn				
225					230					235					240				
Leu	Lys	Lys	Leu	Arg	Ala	Arg	Ser	Thr	Tyr	Asn	Leu	Lys	Lys	Leu	Pro				
				245					250						255				
Thr	Leu	Glu	Lys	Leu	Val	Ala	Leu	Met	Glu	Ala	Ser	Leu	Thr	Tyr	Pro				
			260					265						270					
Ser	His	Cys	Cys	Ala	Phe	Ala	Asn	Trp	Arg	Arg	Gln	Ile	Ser	Glu	Leu				
		275					280					285							
His	Pro	Ile	Cys	Asn	Lys	Ser	Ile	Leu	Arg	Gln	Glu	Val	Asp	Tyr	Met				
	290					295					300								
Thr	Gln	Ala	Arg	Gly	Gln	Arg	Ser	Ser	Leu	Ala	Glu	Asp	Asn	Glu	Ser				
305					310					315					320				
Ser	Tyr	Ser	Arg	Gly	Phe	Asp	Met	Thr	Tyr	Thr	Glu	Phe	Asp	Tyr	Asp				
				325					330					335					
Leu	Cys	Asn	Glu	Val	Val	Asp	Val	Thr	Cys	Ser	Pro	Lys	Pro	Asp	Ala				
			340					345					350						
Phe	Asn	Pro	Cys	Glu	Asp	Ile	Met	Gly	Tyr	Asn	Ile	Leu	Arg	Val	Leu				
		355					360					365							
Ile	Trp	Phe	Ile	Ser	Ile	Leu	Ala	Ile	Thr	Gly	Asn	Ile	Ile	Val	Leu				
	370					375					380								
Val	Ile	Leu	Thr	Thr	Ser	Gln	Tyr	Lys	Leu	Thr	Val	Pro	Arg	Phe	Leu				
385					390					395					400				
Met	Cys	Asn	Leu	Ala	Phe	Ala	Asp	Leu	Cys	Ile	Gly	Ile	Tyr	Leu	Leu				
				405					410					415					

Leu Ile Ala Ser Val Asp Ile His Thr Lys Ser Gln Tyr His Asn Tyr
420 425 430

Ala Ile Asp Trp Gln Thr Gly Ala Gly Cys Asp Ala Ala Gly Phe Phe
435 440 445

Thr Val Phe Ala Ser Glu Leu Ser Val Tyr Thr Leu Thr Ala Ile Thr
450 455 460

Leu Glu Arg Trp His Thr Ile Thr His Ala Met Gln Leu Asp Cys Lys
465 470 475 480

Val Gln Leu Arg His Ala Ala Ser Val Met Val Met Gly Trp Ile Phe
485 490 495

Ala Phe Ala Ala Ala Leu Phe Pro Ile Phe Gly Ile Ser Ser Tyr Met
500 505 510

Lys Val Ser Ile Cys Leu Pro Met Asp Ile Asp Ser Pro Leu Ser Gln
515 520 525

Leu Tyr Val Met Ser Leu Leu Val Leu Asn Val Leu Ala Phe Val Val
530 535 540

Ile Cys Gly Cys Tyr Ile His Ile Tyr Leu Thr Val Arg Asn Pro Asn
545 550 555 560

Ile Val Ser Ser Ser Ser Asp Thr Arg Ile Ala Lys Arg Met Ala Met
565 570 575

Leu Ile Phe Thr Asp Phe Leu Cys Met Ala Pro Ile Ser Phe Phe Ala
580 585 590

Ile Ser Ala Ser Leu Lys Val Pro Leu Ile Thr Val Ser Lys Ala Lys
595 600 605

Ile Leu Leu Val Leu Phe His Pro Ile Asn Ser Cys Ala Asn Pro Phe
610 615 620

Leu Tyr Ala Ile Phe Thr Lys Asn Phe Arg Arg Asp Phe Phe Ile Leu
625 630 635 640

Leu Ser Lys Cys Gly Cys Tyr Glu Met Gln Ala Gln Ile Tyr Arg Thr
645 650 655

Glu Thr Ser Ser Thr Val His Asn Thr His Pro Arg Asn Gly His Cys
 660 665 670

Ser Ser Ala Pro Arg Val Thr Ser Gly Ser Thr Tyr Ile Leu Val Pro
 675 680 685

Leu Ser His Leu Ala Gln Asn
 690 695

<210> 23
 <211> 700
 <212> PRT
 <213> Rattus sp.

<400> 23

Met Gly Arg Arg Val Pro Ala Leu Arg Gln Leu Leu Val Leu Ala Val
 1 5 10 15

Leu Leu Leu Lys Pro Ser Gln Leu Gln Ser Arg Glu Leu Ser Gly Ser
 20 25 30

Arg Cys Pro Glu Pro Cys Asp Cys Ala Pro Asp Gly Ala Leu Arg Cys
 35 40 45

Pro Gly Pro Arg Ala Gly Leu Ala Arg Leu Ser Leu Thr Tyr Leu Pro
 50 55 60

Val Lys Val Ile Pro Ser Gln Ala Phe Arg Gly Leu Asn Glu Val Val
 65 70 75 80

Lys Ile Glu Ile Ser Gln Ser Asp Ser Leu Glu Arg Ile Glu Ala Asn
 85 90 95

Ala Phe Asp Asn Leu Leu Asn Leu Ser Glu Leu Leu Ile Gln Asn Thr
 100 105 110

Lys Asn Leu Leu Tyr Ile Glu Pro Gly Ala Phe Thr Asn Leu Pro Arg
 115 120 125

Leu Lys Tyr Leu Ser Ile Cys Asn Thr Gly Ile Arg Thr Leu Pro Asp
 130 135 140

Val Thr Lys Ile Ser Ser Ser Glu Phe Asn Phe Ile Leu Glu Ile Cys
 145 150 155 160

Asp Asn Leu His Ile Thr Thr Ile Pro Gly Asn Ala Phe Gln Gly Met

Leu Met Cys Asn Leu Ser Phe Ala Asp Phe Cys Met Gly Leu Tyr Leu
405 410 415

Leu Leu Ile Ala Ser Val Asp Ser Gln Thr Lys Gly Gln Tyr Tyr Asn
 420 425 430

His Ala Ile Asp Trp Gln Thr Gly Ser Gly Cys Gly Ala Ala Gly Phe
 435 440 445

Phe Thr Val Phe Ala Ser Glu Leu Ser Val Tyr Thr Leu Thr Val Ile
 450 455 460

Thr Leu Glu Arg Trp His Thr Ile Thr Tyr Ala Val Gln Leu Asp Gln
 465 470 475 480

Lys Leu Arg Leu Arg His Ala Ile Pro Ile Met Leu Gly Gly Trp Leu
 485 490 495

Phe Ser Thr Leu Ile Ala Thr Met Pro Leu Val Gly Ile Ser Asn Tyr
 500 505 510

Met Lys Val Ser Ile Cys Leu Pro Met Asp Val Glu Ser Thr Leu Ser
 515 520 525

Gln Val Tyr Ile Leu Ser Ile Leu Ile Leu Asn Val Val Ala Phe Val
 530 535 540

Val Ile Cys Ala Cys Tyr Ile Arg Ile Tyr Phe Ala Val Gln Asn Pro
 545 550 555 560

Glu Leu Thr Ala Pro Asn Lys Asp Thr Lys Ile Ala Lys Lys Met Ala
 565 570 575

Ile Leu Ile Phe Thr Asp Phe Thr Cys Met Ala Pro Ile Ser Phe Phe
 580 585 590

Ala Ile Ser Ala Ala Phe Lys Val Pro Leu Ile Thr Val Thr Asn Ser
 595 600 605

Lys Ile Leu Leu Val Leu Phe Tyr Pro Val Asn Ser Cys Ala Asn Pro
 610 615 620

Phe Leu Tyr Ala Ile Phe Thr Lys Ala Phe Gln Arg Asp Phe Leu Leu
 625 630 635 640

Leu Leu Ser Arg Phe Gly Cys Cys Lys Arg Arg Ala Glu Leu Tyr Arg
 645 650 655

19/22

Arg Lys Glu Phe Ser Ala Tyr Thr Ser Asn Cys Lys Asn Gly Phe Pro
 660 665 670

Gly Ala Ser Lys Pro Ser Gln Ala Thr Leu Lys Leu Ser Thr Val His
 675 680 685

Cys Gln Gln Pro Ile Pro Pro Arg Ala Leu Thr His
 690 695 700

<210> 24
 <211> 699
 <212> PRT
 <213> Homo sapiens

<400> 24

Met Lys Gln Arg Phe Ser Ala Leu Gln Leu Leu Lys Leu Leu Leu Leu
 1 5 10 15

Leu Gln Pro Pro Leu Pro Arg Ala Leu Arg Glu Ala Leu Cys Pro Glu
 20 25 30

Pro Cys Asn Cys Val Pro Asp Gly Ala Leu Arg Cys Pro Gly Pro Thr
 35 40 45

Ala Gly Leu Thr Arg Leu Ser Leu Ala Tyr Leu Pro Val Lys Val Ile
 50 55 60

Pro Ser Gln Ala Phe Arg Gly Leu Asn Glu Val Ile Lys Ile Glu Ile
 65 70 75 80

Ser Gln Ile Asp Ser Leu Glu Arg Ile Glu Ala Asn Ala Phe Asp Asn
 85 90 95

Leu Leu Asn Leu Ser Glu Ile Leu Ile Gln Asn Thr Lys Asn Leu Arg
 100 105 110

Tyr Ile Glu Pro Gly Ala Phe Ile Asn Leu Pro Gly Leu Lys Tyr Leu
 115 120 125

Ser Ile Cys Asn Thr Gly Ile Arg Lys Phe Pro Asp Val Thr Lys Val
 130 135 140

Phe Ser Ser Glu Ser Asn Phe Ile Leu Glu Ile Cys Asp Asn Leu His
 145 150 155 160

Ile Thr Thr Ile Pro Gly Asn Ala Phe Gln Gly Met Asn Asn Glu Ser

165 170 175
 Val Thr Leu Lys Leu Tyr Gly Asn Gly Phe Glu Glu Val Gln Ser His
 180 185 190
 Ala Phe Asn Gly Thr Thr Leu Thr Ser Leu Glu Leu Lys Glu Asn Val
 195 200 205
 His Leu Glu Lys Met His Asn Gly Ala Phe Arg Gly Ala Thr Gly Pro
 210 215 220
 Lys Thr Leu Asp Ile Ser Ser Thr Lys Leu Gln Ala Leu Pro Ser Tyr
 225 230 235 240
 Gly Leu Glu Ser Ile Gln Arg Leu Ile Ala Thr Ser Ser Tyr Ser Leu
 245 250 255
 Lys Lys Leu Pro Ser Arg Glu Thr Phe Val Asn Leu Leu Glu Ala Thr
 260 265 270
 Leu Thr Tyr Pro Ser His Cys Cys Ala Phe Arg Asn Leu Pro Thr Lys
 275 280 285
 Glu Gln Asn Phe Ser His Ser Ile Ser Glu Asn Phe Ser Lys Gln Cys
 290 295 300
 Glu Ser Thr Val Arg Lys Val Ser Asn Lys Thr Leu Tyr Ser Ser Met
 305 310 315 320
 Leu Ala Glu Ser Glu Leu Ser Gly Trp Asp Tyr Glu Tyr Gly Phe Cys
 325 330 335
 Leu Pro Lys Thr Pro Arg Cys Ala Pro Glu Pro Asp Ala Phe Asn Pro
 340 345 350
 Cys Glu Asp Ile Met Gly Tyr Asp Phe Leu Arg Val Leu Ile Trp Leu
 355 360 365
 Ile Asn Ile Leu Ala Ile Met Gly Asn Met Thr Val Leu Phe Val Leu
 370 375 380
 Leu Thr Ser Arg Tyr Lys Leu Thr Val Pro Arg Phe Leu Met Cys Asn
 385 390 395 400
 Leu Ser Phe Ala Asp Phe Cys Met Gly Leu Tyr Leu Leu Leu Ile Ala
 405 410 415

Ser Val Asp Ser Gln Thr Lys Gly Gln Tyr Tyr Asn His Ala Ile Asp
 420 425 430

Trp Gln Thr Gly Ser Gly Cys Ser Thr Ala Gly Phe Phe Thr Val Phe
 435 440 445

Ala Ser Glu Leu Ser Val Tyr Thr Leu Thr Val Ile Thr Leu Glu Arg
 450 455 460

Trp His Thr Ile Thr Tyr Ala Ile His Leu Asp Gln Lys Leu Arg Leu
 465 470 475 480

Arg His Ala Ile Leu Ile Met Leu Gly Gly Trp Leu Phe Ser Ser Leu
 485 490 495

Ile Ala Met Leu Pro Leu Val Gly Val Ser Asn Tyr Met Lys Val Ser
 500 505 510

Ile Cys Phe Pro Met Asp Val Glu Thr Thr Leu Ser Gln Val Tyr Ile
 515 520 525

Leu Thr Ile Leu Ile Leu Asn Val Val Ala Phe Phe Ile Ile Cys Ala
 530 535 540

Cys Tyr Ile Lys Ile Tyr Phe Ala Val Arg Asn Pro Glu Leu Met Ala
 545 550 555 560

Thr Asn Lys Asp Thr Lys Ile Ala Lys Lys Met Ala Ile Leu Ile Phe
 565 570 575

Thr Asp Phe Thr Cys Met Ala Pro Ile Ser Phe Phe Ala Ile Ser Ala
 580 585 590

Ala Phe Lys Val Pro Leu Ile Thr Val Thr Asn Ser Lys Val Leu Leu
 595 600 605

Val Leu Phe Tyr Pro Ile Asn Ser Cys Ala Asn Pro Phe Leu Tyr Ala
 610 615 620

Ile Phe Thr Lys Thr Phe Gln Arg Asp Phe Phe Leu Leu Leu Ser Lys
 625 630 635 640

Phe Gly Cys Cys Lys Arg Arg Ala Glu Leu Tyr Arg Arg Lys Asp Phe
 645 650 655

Ser Ala Tyr Thr Ser Asn Cys Lys Asn Gly Phe Thr Gly Ser Asn Lys
660 665 670

Pro Ser Gln Ser Thr Leu Lys Leu Ser Thr Leu His Cys Gln Gly Thr
675 680 685

Ala Leu Leu Asp Lys Thr Arg Tyr Thr Glu Cys
690 695